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Report No. 12

Annual Progress Report

BIOCHEMICAL CHANGES IN TISSUES DURING INFECTIOUS ILLNESS:
THE BIOENERGETICS OF INFECTION AND EXERCISE

by

Robert L. Squibb, Ph.D.

June 1977

(For the period 1 July 1976 to 30 June 1977)

Supported by

U. S. ARMY MEDICAL RESEARCH AND DEVELOPMENT COMMAND

Washington, D. C. 20314

Contract No. DA-49-193-MD-2694

Rutgers - The State University,
New Brunswick, New Jersey 08903

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Exercise has been categorized as forced, voluntary and involuntary. Treadmills and running wheels have been modified so that investigations can be made of each type of exercise in interaction with infectious disease. Rats exercising by voluntarily turning treadmills on and off had a high preference for treadmill speeds of 24.4 m/min which persisted despite changing workloads. (increasing the slope of the treadmills from 0° to 18°). These data are vital for the design of future experiments involving voluntary and forced exercise interactions with infectious disease. Preliminary studies showed that rats		

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infected with S. typhimurium and given voluntary access to running wheels had less disease involvement and lower mortality rates than subjects not given access to running wheels.

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FOREWORD

The role of exercise in the physical well-being of humans is of vital importance to Military Science. A recent survey of the literature revealed that very little research is being conducted on the interaction of exercise and disease, in spite of its obvious importance.

In conducting the research described in this report, the investigator adhered to the "Guide for Laboratory Animal Facilities and Care" as promulgated by the Committee on the Guide for Laboratory Animal Facilities and Care of the Institute of Laboratory Animal Resources, National Academy of Sciences-National Research Council.

SUMMARY

During this 1976-77 research year, exercise has been categorized as forced, voluntary or involuntary. It was hypothesized that biochemical changes in noninfected and infected tissues, physical well-being and survival of infected subjects would be affected differently by each kind of exercise prior to, during and following infection.

Treadmills and running wheels have been modified or designed so that future studies on exercise x infection may be undertaken with each category of exercise.

Work accomplished shows that when rats were allowed to run on a treadmill voluntarily they had repeated preference for a treadmill speed of 24.4 m/min which persisted despite increasing workloads, e.g., changing the slopes of the treadmill from 0 to 18°. These data will be the baseline from which to study exercise x disease interactions.

Preliminary studies recently concluded show that voluntary exercise of rats in running wheels significantly interacts with amount of running, energy source and expenditures, and beneficial effects on the physical well-being and survival of subjects with S. typhimurium.

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INTRODUCTION

Based on data obtained during the current reporting period, it has become obvious that exercise should be examined on the basis of 1) the kind of exercise performed, e.g., forced, voluntary, or involuntary when running wheels are used; and 2) how much of the exercise or activity takes place in the wheel and how much during the so-called "inactive" period when the subject is in the home cage.

This means that the equipment used for these observations should be such that readouts can be obtained for each category of exercise in order to examine the hypothesis that "each type of exercise will have a different interaction with an infectious disease and each will result in significant differences in the biochemistry of target tissues."

The present report describes

- 1) Modification of an activity wheel so that observations can be recorded of when an animal is in the running wheel and when he is in the home cage;
- 2) A preliminary evaluation of the behavioral response to exercise of the rat on a special treadmill designed so that it can be operated voluntarily or programmed for forced exercise of animals during an infection;
- 3) Preliminary observations on voluntary exercise (running wheels) x S. typhimurium interactions in rats;
- 4) The chickens' response to different types of energy sources (natural corn oil and a synthetic ester of butanediol) during recovery from a viral infection.

WORKING DEFINITIONS OF "EXERCISE" USING RAT AND CHICK MODELS

Preliminary analysis of the data observed during the course of this research year (1976-77) indicated that the term "exercise" must be more definitive and not all-encompassing. As a consequence, exercise has been partitioned into three categories, each of vital significance to the military:

1. Forced exercise: a clear-cut classification wherein the animal model is forced to perform totally against its will, thereby subjecting the animal's emotions and metabolic machinery to the greatest amount of stress.
2. Voluntary exercise: Under this category the animal model turns a running wheel or presses a bar switch to operate a treadmill whenever it wishes to do so.
3. Involuntary exercises: This form of exercise is a metabolic reaction to or results from either endogenous (hunger, diet components and contaminants, disease, etc.) or exogenous (noise, temperature) inputs. Hyperactivity in humans and the spontaneous activity reaction of animals to hunger falls into this category.

1. EVALUATION OF EXERCISE APPARATUS FOR RATS AND CHICKS

During the 1976-77 research year Wahmann running wheels and specially designed treadmills were selected to evaluate their usefulness in subsequent studies of the interaction of disease x forced, voluntary or involuntary exercise.

A. Voluntary Exercise of Rats on Treadmills

The treadmills were designed to be operated voluntarily by animals and consisted of two table-top belt sanders; a fine grained cork belt provided the running surface. Each apparatus was adjustable for a wide selection of speeds and slopes. A plexiglass compartment was mounted over the entire running surface with a bar press lever for activating the treadmill placed on the front panel for convenient access by the animal. Four photocell light beams, mounted 5 and 7 inches back from the front panel, were positioned so that the treadmill remained in motion as long as any of the four beams were interrupted by the rat. The treadmill would cease operation when the animal voluntarily stopped running and was carried to the rear of the compartment. Additional equipment consisted of a cumulative meter which timed the duration of running activity; a burst counter to observe total number of running bursts; and a Gerbrands time event recorder which provided data for

the calculation of the temporal aspects of the running patterns.

Nine male rats of the Sprague-Dawley strain were fed a stock diet and water ad libitum for 87 days. The feed ration was then restricted so that body weights averaging 203 ± 2 g absolute were held constant for the entire experiment of 7 trials by increasing or decreasing the daily allotments of food for each rat. Maintaining the rats at constant body weight was necessary to induce them to run voluntarily on the treadmills.

All rats were housed individually in an isolated room which contained both the cages and treadmill apparatus. Lighting was set for 12 hrs dark/12 hrs light, with the dark phase starting at 0800 hrs. All trials were scheduled during the dark period.

For three days prior to the start of the first trial, each rat had a daily 90-min session in the treadmill apparatus for habituation and self-training of bar pressing to operate the treadmill. The association between the manipulation of the bar press lever and the voluntary operation of the treadmill was learned within this preliminary period.

The trials were run consecutively, each involving a change in speed and slope of the treadmill. The rats were placed on the treadmill at the same hour every day for a 90-min session and then returned to the home cage. Body weights were obtained prior to exercise and all animals were fed immediately after their running session. The experimental design and duration of each trial are shown in table 1.

Trials 1 and 2 were designed to determine whether a rat would show a preference for a particular assigned speed over a range of 6 to 73 m/min, with slope at 0° . In trial 1 the speeds were assigned in ascending order and in trial 2 in random order to ensure that selections were not associated with order of presentation. During trial 3 the rats were held without access to the treadmills for a 12-day period and the amounts of diet needed to maintain 203 ± 2 g body weight were recorded.

The objective of trials 4-7 was to observe whether the imposition of "workloads" (increasing slopes) would affect patterns of running and increase the feed required to maintain body weights constant. In these trials the 6.1 and 73.2 m/min speeds were discontinued and 12.2, 24.4 and 48.8 m/min were offered in random order with the slopes of the treadmills changed in the following sequence: 0, 9, 18 and 27° (table 1).

Figure 1 shows the average time spent voluntarily exercising on treadmills set at different speeds and slopes. Except for trial 7 (27° slope), overall patterns of activity showed that maximum running time occurred at a treadmill speed of 24.4 m/min. As slopes were increased, time spent running at 24.4 m/min decreased in decremental order.

The histograms in Fig. 2 typify the running patterns for the 90-min sessions at treadmill speeds of 12.2, 24.4 and 48.8 m/min and 0° slope. The most frequent bursts at 24.4 m/min treadmill speed were 21-24 sec

in duration; average inter-burst time was 20 sec. In all trials as speeds and slopes were increased the frequency of short-duration running bursts increased.

The data show that rats maintained at constant body weight and with the option of daily 90-min periods of voluntary operation of a treadmill had repeated, definite preferences for speeds. This repeatability of selection of a particular speed was unaffected by 1) ascending or random presentation of treadmill speeds; 2) a rest period of 12 days which did not diminish or extinguish this preference; and 3) a change in workloads, i.e., increasing slopes to 18°.

Running bursts, which relate directly to oxygen consumption, showed a spectrum of activity that changed according to speeds offered (Fig. 2). At a treadmill speed of 24.4 m/min and 0° slope the distribution of the duration of running bursts was symmetrical. This pattern of activity changed to a higher frequency of short-duration bursts at slower speeds and to a considerably higher frequency of short bursts above speeds of 24.4 m/min. These patterns were characteristic of treadmill conditions regardless of sequential or random changes of speeds and slopes.

Since voluntary running is highly selective and motivated, one may speculate that disease involvement with the metabolic "machinery" would change either baseline patterns of running bursts or levels of activity or both.

Table 1. Schedule of treadmill speeds and slopes for each trial

Trial	Duration of trial ^{1/} days	Order of presentation of	
		Treadmill speeds meters/min	Treadmill slopes degrees
1	35	6.1, 12.2, 24.4, 48.8, 73.2 ^{2/}	0
2	20	24.4, 6.1, 48.8, 12.2, 73.2 ^{3/}	0
3 ^{4/}	12	N/A	N/A
4	12	12.2, 48.8, 24.4 ^{3/}	0
5	12	24.4, 48.8, 12.2 ^{3/}	9
6	12	12.2, 48.8, 24.4 ^{3/}	18
7	12	48.8, 24.4, 12.2 ^{3/}	27

1/ 90-min session per rat per day

2/ Assigned sequence

3/ Randomly assigned sequence

4/ Rats kept in individual cages without access to treadmills

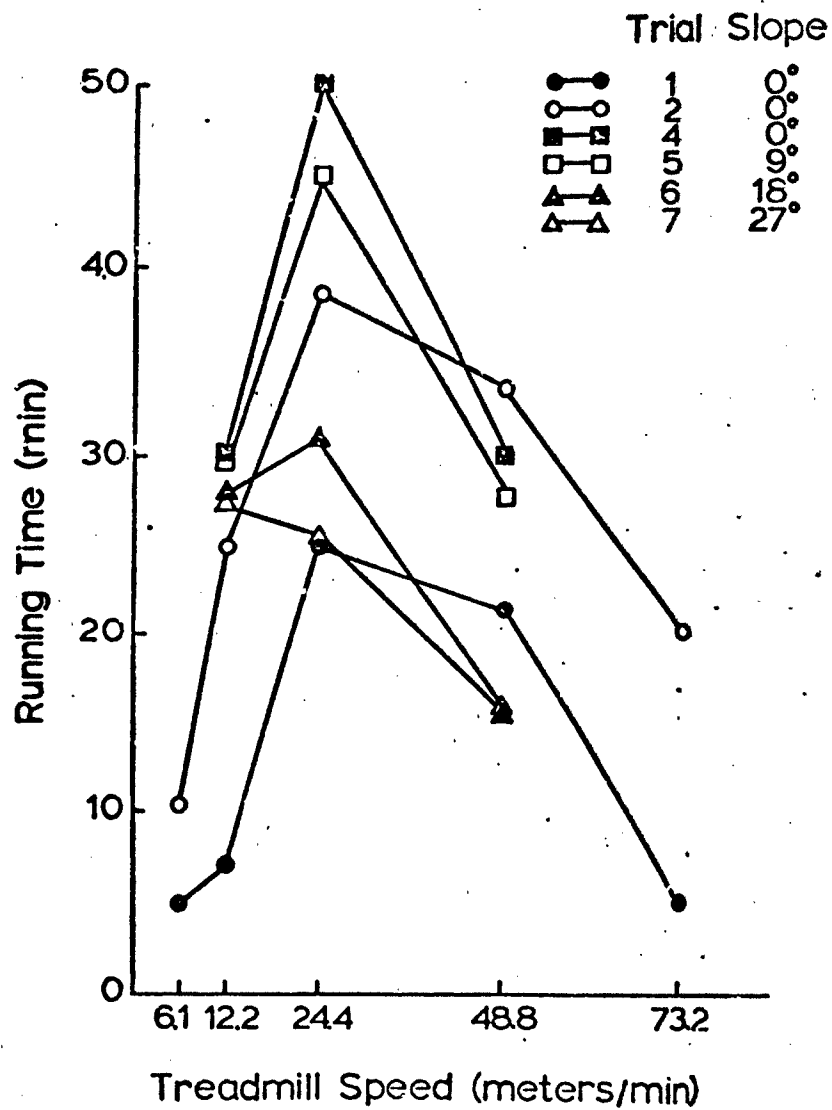


Fig. 1. Average time run (min) for combination of assigned treadmill speeds and slopes. Trial 3 was a 12-day period without access to the treadmills.

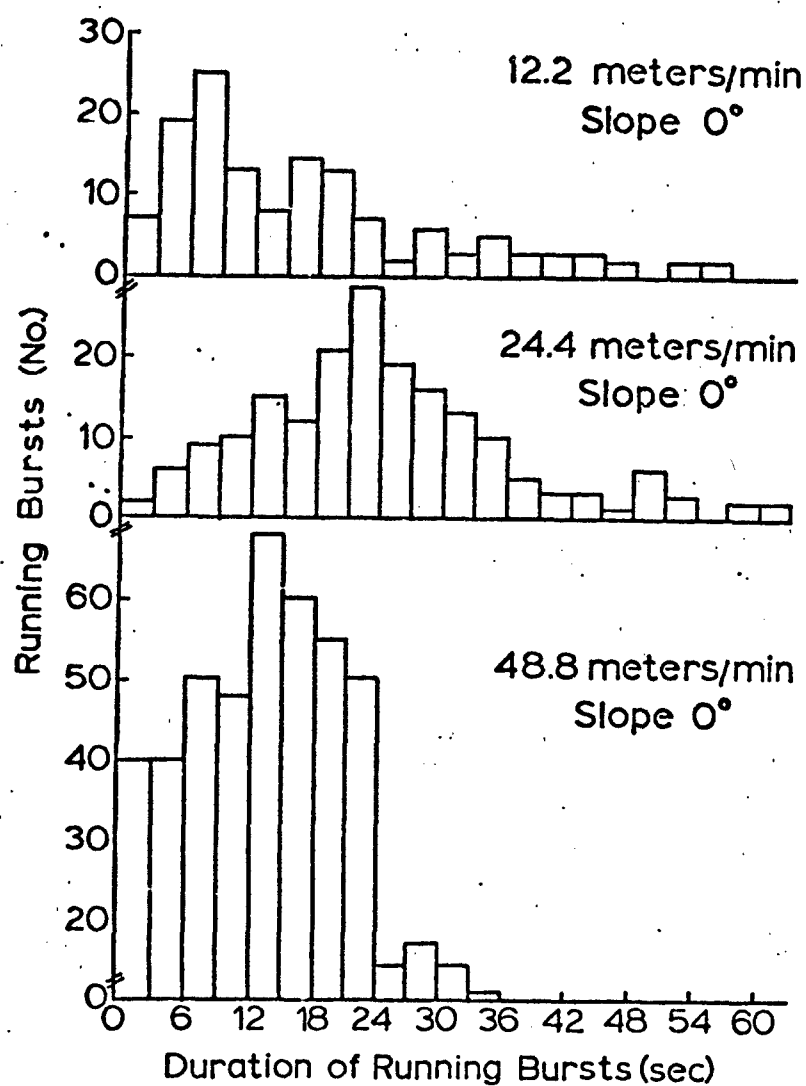


Fig. 2. Histogram of running burst numbers and duration typical for 90-min sessions at treadmill speeds of 12.2, 24.4 and 48.8 m/min, slope 0°.

II. STANDARDIZATION OF PROCEDURE FOR INDUCING SPONTANEOUS EXERCISE

A standardized procedure has been developed for inducing spontaneous exercise in rats or chicks so that more precise observations on the effects of exercise x infection will be possible.

In the procedure, weanling rats are given a stock diet ad libitum until they weigh 70-80 g and are then fed 5 g/rat/day. The shift to restricted feeding causes the animal to immediately become hyperactive and to lose weight for approximately 4 days at which time body mass stabilizes at 60-70 g. This restriction does not prevent an animal from returning to its genetic potential for size when restored to an ad libitum regimen, providing the diet is complete in all essentials.

Two studies, differing in preparation of the animals prior to induction of spontaneous activity, are presented here to illustrate the procedure. All animals were noninfected; two different food toxicants were used as insults to metabolism instead of an infectious disease.

In the first series of studies weanling male rats were housed individually in Wahlmann running wheels and maintained on a 12 hour light/dark schedule with lights on at 0800 hours. The animals were given ad libitum iron-deficient or supplemented (reference control) diets with and without dioscin. This naturally occurring toxicant was included at 0.5% of dry weight, a level calculated to be equal to that consumed by humans. All rats were continued on the experimental diets ad libitum until day 12; at this time there were no significant differences in average body weights (74 g) or running activity between the treatment groups.

On day 12 spontaneous activity was induced by the standardized procedure described above. Daily wheel turns (WTs) of the reference control group immediately increased from 400 to over 10,000/rat by day 17. Compared to the reference values, WTs progressively declined in the other groups in the following treatment order: dietary dioscin extract (DE), iron-deficient, and the combination of DE and iron deficiency (Fig. 3).

In the next studies, 22-day-old male rats were fed a reference diet ad libitum until they reached average weights of 73 g by day 13. At this time spontaneous activity was again induced by the standardized procedure and the resulting WTs observed for a 3-day period. These data were used to form four experimental groups matched for activity levels. On day 16, 4 levels of cadmium, 0 (controls), 61, 122 and 244 ppm, were added to the reference diet and WTs and body weights recorded daily until day 25.

Immediately following the interaction of cadmium with the induced spontaneous activity, a hyper reaction among the cadmium groups was indicated by significant short-term increases in daily WTs above the reference control group (Fig. 4). Following this "alarm" reaction, which maximized by day 20, WTs decreased to below baseline reference levels for the remaining 4 days of the trial. During this hypoactive interval, running wheel responses to the cadmium toxicities showed

indications of dose response. Analysis of the livers obtained at the end of the trial showed that while liver weights were not significantly different between groups, the ppm of detectable cadmium per gram of liver were: 0 ppm, nondetectable; 0.99 for the 61 ppm; 3.8 for the 122 ppm; and 8.2 for the 244 ppm group. Linearity of the response was significant.

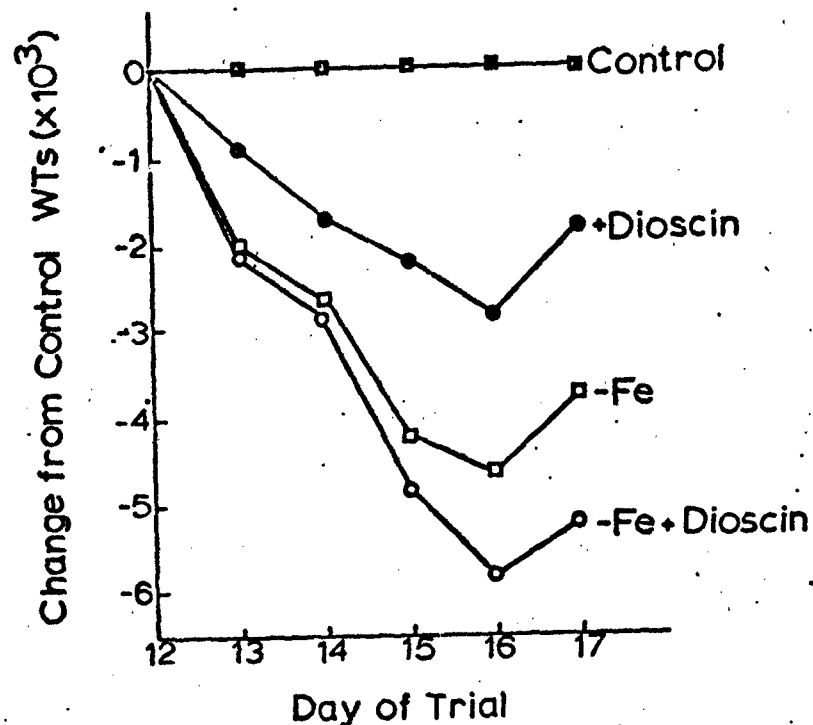


Fig. 3. Wheel turns hypo to control values following the induction of spontaneous activity on day 12 in rats conditioned for 12 days on an iron-deficient diet with and without the addition of iron and a crude extract of dioscin. Data combined for 3 replicates, each having 9 rats per treatment group.

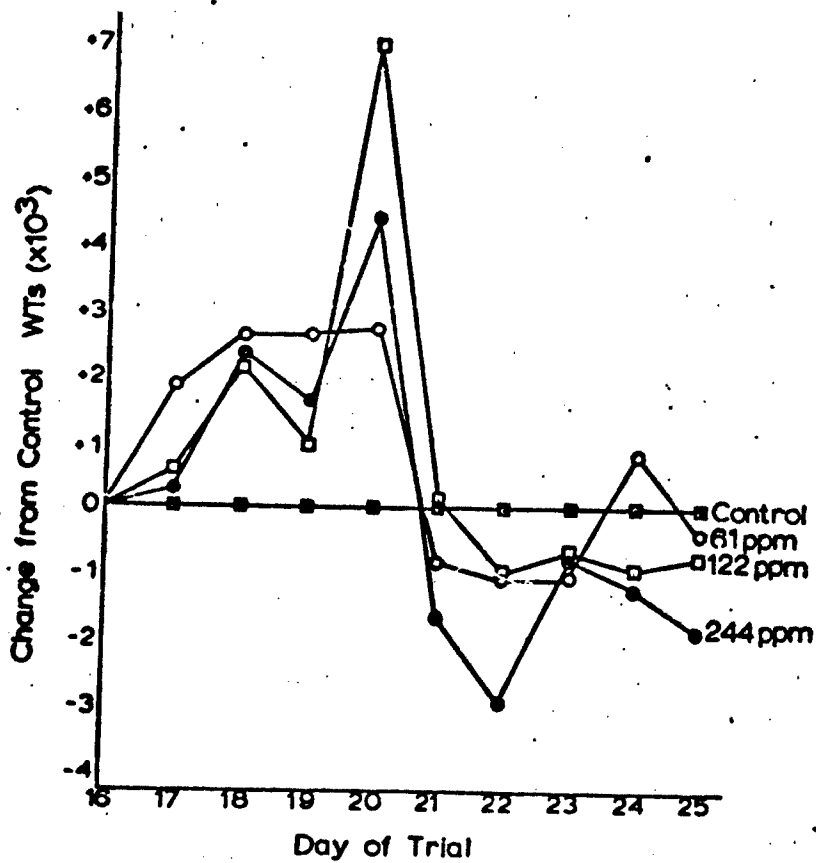


Fig. 4. Wheel turns hyper and hypo to control values following the induction of spontaneous activity and the interaction of cadmium at 0 (controls), 61, 122 and 244 ppm on day 16. Data combined for 2 replicates each having 9 rats per treatment group.

III. VOLUNTARY WHEEL RUNNING IN RATS INFECTED WITH S. TYPHIMURIUM

In this experiment the previously described energy model of Squibb, Solotorovsky and Beisel was used to induce hyperactivity (category 3 of partition of exercise). The study was extended to include comparisons of two dietary energy sources - 10% corn oil or 10% of 1,3 butanediol-1,3 dioctanoate (BDDO), synthesized especially for this study; the BDDO has a metabolizable energy content equivalent to corn oil. The experimental design was such that for each energy source noninfected and S. typhimurium-infected groups were included with and without voluntary access to running wheels. In all, there were 8 groups with 11 rats/group.

As shown in table 2, weight gains were higher in the non-exercising rats; this is to be expected and reflects the leaner body mass of the animals exercising voluntarily. There was no mortality in the infected animals when given access to running wheels whereas in their non-exercising counterparts 3 out of 44 died in the 12-day trial period.

Table 2. Effect of S. typhimurium and voluntary exercise on weight gains and mortality of rats fed corn oil or BDDO^{1/}

Treatment	No. animals	Net weight gain, 12 days g	Mortality %
<u>Non-exercising</u>			
Corn oil, noninfected	11	39.3	0
Corn oil, infected	11	35.1	9
BDDO, noninfected	11	36.9	0
BDDO, infected	11	30.6	18
<u>Exercising^{2/}</u>			
Corn oil, noninfected	11	33.4	0
Corn oil, infected	11	30.4	0
BDDO, noninfected	11	27.1	0
BDDO, infected	11	25.4	0

^{1/} BDDO = 1,3 butanediol-1,3 dioctanoate

^{2/} Constant access to running wheels

Starting on the 4th day of the trial the noninfected BDDO rats ran significantly more than those on the corn oil diet whereas in the infected group the BDDO rats ran slightly less. Infected rats given corn oil ran on a par with their controls, but the BDDO resulted in the infected animals running significantly less than their respective controls, a clear interaction of energy source, exercise and disease. The data are shown in table 3. As a corollary there was a significantly greater energy cost for exercise and exercise x disease in the BDDO group (table 4).

Table 3. Daily wheel running in rats fed corn oil or BDDO^{1/} and infected with *S. typhimurium*.

Day of trial	Noninfected		Infected	
	Corn oil	BDDO	Corn oil	BDDO
	number of wheel turns			
1	1,608 ^{2/}	1,585	2,050	1,231
2	1,974	1,522	1,816	1,672
3	2,172	2,128	2,379	1,723
4	1,751	2,274	3,034	1,981
5	1,445	2,014	1,660	1,823
6	1,593	2,876	1,283	1,114
7	1,522	2,608	1,711	1,684
8	1,721	2,878	1,765	1,702
9	3,109	4,833	2,466	2,173
10	2,486	3,702	2,375	1,792
11	2,803	3,812	2,596	2,456
12	2,740	3,756	2,406	1,789
Total	24,924	33,988	25,541	21,140

^{1/} BDDO = 1,3 butanediol-1,3 dioctanoate

^{2/} n = 11 rats per group

Table 4. Energy demands of exercise and *S. typhimurium* in rats fed dietary corn oil or BDDO^{1/}

Treatment	kcal's metabolizable energy per 100 g body mass	
	Corn oil	BDDO
Exercise ^{2/}	30	73
Infection, <i>S. typhimurium</i>	12	8
Exercise x Infection	27	99
Exercise + infection	39	107

^{1/} BDDO = 1, 3 butanediol-1,3 dioctanoate

^{2/} Constant access to running wheels

IV. OBSERVATIONS ON RECOVERY FROM A NEWCASTLE DISEASE VIRUS INFECTION

Recovery from infectious disease is of critical importance to military operations. The preliminary studies reported here were undertaken to establish methodology and baseline data to be used later to evaluate the effects of forced and/or voluntary exercise on animals recovering from a virus infection.

In these studies, susceptible chicks were inoculated with Newcastle disease virus at a level that would produce 100% infection but no more than 30% mortality, thus indicating the severity of the infection in the chicks as they entered the recovery phase. Immediately at the end of the period of overt illness (6 days post inoculation), the "recovering" birds were assigned on the basis of body weights and physical appearance to 4 groups of 15 each. Three of the groups were placed on a restricted feeding schedule and fed either a low energy diet, a 10% corn oil diet (high energy) or one containing 10% of 1,3-butanediol-1,3 dioctanoate (BDDO), a synthetic energy source equivalent to corn oil. One group was given the corn oil diet ad libitum.

At the end of a 10-day recovery period the animals on the low energy diet had increased their body weights by 4%; those on the corn oil gained 28% and on the BDDO 30%. Chicks on the ad libitum corn oil diet were 85% above their initial weight 10 days earlier.

At the end of this 10-day recovery period half the chicks in each group were sacrificed at 0800 hours and serum and livers obtained; the other half were sacrificed at 1500 hours the same day. Biochemical analyses of the tissues are not complete at this time. However, as shown in table 5, total quantities of glycogen were significantly higher in the chicks on the BDDO diet than in any of the other groups. The striking differences in values of the various parameters at 0800 and 1500 hours can be seen in the table also, evidence once again of the necessity of considering the phenomenon of bioclocks in experimental designs and time of sampling tissues.

V. MODIFICATION OF RUNNING WHEEL TO PERMIT DIFFERENTIATING ACTIVITY IN WHEEL FROM THAT IN HOME CAGE

The description of the modification is as follows: the complete exercise monitor and information processing system consists of a Wahmann activity wheel with an attached tilt cage having the following features: a) three movement detector switches, one for sensing wheel turns plus two for home cage movements; and b) an information processor with transistor-transistor integrated electronic circuitry designed to process data via 4 channels with TTL logics and to interface activity data from the equipment with standard recording devices such as time event recorders and electronic counters.

Table 5. Body and liver weights and biochemical data from livers of chicks recovering from a Newcastle disease virus infection and fed dietary corn oil or BDDO on a restricted or ad libitum regimen.

Parameter	Restricted regimen of energy model ^{1/}						Ad libitum	
	Low energy			High energy			High energy	
	0800	1500		0800	1500	10% BDDO ^{2/}	0800	1500
Body weight (g)	204.3	240.5		247.7	282.0	251.1	289.1	
Liver weight (g)	6.3	8.1		7.1	8.8	8.0	11.0	355.5
Liver/body (%)	3.1	3.4		2.8	3.1	3.2	3.5	11.0
								3.1
Concentrations - mg/g liver								
DNA	2.06	1.73		2.30	1.91	2.19	1.65	1.92
RNA	12.2	9.4		11.4	10.4	11.9	9.6	11.3
Protein	262	222		256	241	254	205	237
Glucose	0.30	1.14		0.38	0.93	0.46	1.22	0.86
Glycogen	0.14	34.2		1.38	16.4	3.14	39.9	4.50
Total quantities - mg/g x liver weight								
DNA	12.9	14.0		15.7	16.8	17.6	18.2	21.2
RNA	76.4	76.2		80.5	91.2	95.9	105.2	124.9
Protein	1640	1798		1805	2116	2042	2255	2614
Glucose	1.9	9.2		2.7	8.2	3.7	13.4	9.5
Glycogen	0.9	277.0		9.7	144.0	25.2	438.9	49.6
RNA/DNA	5.92	5.44		5.12	5.44	5.45	5.79	5.90
Protein/DNA	127	128		115	126	116	124	123
Glucose/DNA	0.15	0.66		0.17	0.49	0.21	0.74	0.45
Glycogen/DNA	0.07	19.8		3.62	8.60	1.43	24.2	2.3

^{1/} See 1975-76 Annual report for description of model

^{2/} BDDO = 1,3 butanediol-1,3 dioctanoate

^{3/} Tissue samples taken at 0800 and 1500 hours at end of 10-day recovery period

Figure 5 is the systems diagram and schematic of the information processor. Locations where animal movements occur are indicated by the areas marked "activity wheel" and "tilt cage quads". The sensory detectors are labeled S1 to S3. The first two are ultra-sensitive single pole double-throw mercury switches mounted at right angles to each other on top of the tilt cage and the third switch is a cam-operated microswitch mounted adjacent to the wheel drum. Data from the tilt cage switches are processed through four channels, each corresponding to a particular quadrant. Data from the wheel turn sensor is conveyed directly to the recording equipment without having to go through the information processor.

Each channel of the information processor operates in a similar fashion. The following description of the circuit operation for channel 2 quadrant II movements is typical of the other three quadrant channels. A discrete motion by the animal into or within quadrant II causes closures of S1 and S2 at positions B and C, respectively. These ground potentials or 0 volts are passed to input pins 3 and 7 of the 7476, dual JK flip-flop integrated circuit. When the IC receives these 0 inputs, 5 volt positive outputs are produced at pins 14 and 11 and passed to pins 9 and 10 of the 7400 NAND Gate IC. Both inputs must arrive coincident in time for a zero potential output to be produced at pin 8. This output is connected to the base of NPN transistor Q2. The transistor is normally shut-off and non-conductive until it receives a zero potential input from the 7400 IC. When Q2 conducts, relay K2 energizes. Ground potential is then passed via the normally open contacts of this relay to one channel of a time-event recorder and to one electronic cumulative counter. Pulse formers C3, R15, C4 and R16 are for optional interfacing use with relay operated recording equipment. The wheel turn switch operates without the information processor. Data from this sensor is linked directly to the recording instruments, passing ground potential inputs via an optional pulse former.

The novelty of the modifications and advantages over prior instrumentation are: There have been widespread applications and use of activity wheels in the biological and behavioral sciences. Where present activity wheels have only cumulative counters for wheel turns, the features of the present modifications will provide continuous monitoring and recording of wheel turn patterns and exploratory cage crossings by an animal; in other words, total activity of a subject. The modification will also make it possible to obtain data on length of time spent in wheels (i.e., how fast the animal runs) and how much time is spent in the cage.

VI. PUBLICATIONS

- Squibb, R. E., Jr., G. Collier and R. L. Squibb, 1977. Voluntary treadmill activity in rats as a potential indicator of food contaminants. (submitted for publication)
- Squibb, R. E., Jr., R. F. Dawson and R. L. Squibb, 1977. Hyper-hypo responses in spontaneous activity of the rat to food toxicants of natural and accidental origins (submitted for publication)
- Ruttenberg, H. and R. L. Squibb, 1977. Circadian periodicity of nucleic acids and protein in livers of calorie restricted rats. Fed. Proc. 36(3)#4432 (abstract).



Fig. 5. Spontaneous Activity monitor and information processor

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